

SYSTEMIC SCLEROSIS WITH PULMONARY FIBROSIS AND OAT CELL CARCINOMA

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Abstract. A female patient, aged 55, with clinical evidence of systemic sclerosis for 30 years and moderate evidence of pulmonary fibrosis for 8 years, developed a rapidly metastasizing oat cell carcinoma arising from the basal cells of the epithelial lining of cysts in the fibrosed right lower lobe. Metastatic spread was through lymphatics as well as the blood stream. She had been a non-smoker. This is apparently the first report of the association of an oat cell carcinoma and pulmonary fibrosis in systemic sclerosis. It appears that pulmonary cystic changes in areas of fibrosis may give rise to epithelial proliferation of the basal cells, leading to an oat cell carcinoma. In view of this and recent reports of other lung carcinomas in systemic sclerosis it seems advisable to screen patients with systemic sclerosis and significant pulmonary fibrosis carefully and regularly for evidence of lung carcinoma.

Unlike dermatomyositis, systemic sclerosis is not considered to be commonly associated with internal malignancy (16). However, Tomkin (25) drew attention to 16 publications of lung cancer arising in the fibrosed lungs of patients with systemic sclerosis and described a further such patient in whom a squamous cell carcinoma was found, while previous reports had included alveolar cell terminal bronchiolar carcinoma and adenocarcinoma. We have recently found a rapidly metastasizing oat cell carcinoma in a patient with systemic sclerosis and, by no means severe, pulmonary fibrosis.

CASE REPORT

The patient, a married woman of 55, had developed Raynaud's phenomenon at the age of 25 and progressively severe ulceration of her finger tips during her second pregnancy at 36. Bilateral cervical sympathectomy had been carried out when she was 34 in order to relieve her ischaemic pain of hands and Raynaud's phenomenon.

When first seen in 1962, aged 46, she showed the char-

acteristic features of systemic sclerosis, a sharp "pinched" nose, microstomia with radial furrows, thin lips, a smooth forehead and a stiff, hard facial skin. All finger tips were tapered and most showed infected indolent ulceration as well as severe paronychia.

She had slight dysphagia with radiologically demonstrable atonia of the oesophagus and oesophageal reflux. She complained of progressive exertional dyspnoea over the past year and pulmonary function tests showed a diminished compliance and vital capacity but no diffusion defect.

Chest X-ray showed pleural thickening and mild basal pulmonary fibrosis. She was a non-smoker. From 1964 onwards she received a total of 12 low-molecular weight dextran infusions (14, 15) at intervals of up to 10 months. Her digital ulcers healed rapidly and remained healed with surprisingly little scarring. Infusions were given whenever ischaemic pain and Raynaud's phenomenon became more troublesome or whenever there was objective evidence of deteriorating digital blood flow.

Since 1968 she had also been treated with injections of corticotrophin once or twice a week for arthropathy.

Pulmonary function tests and chest X-rays were repeated at least once a year but no evidence of significant changes was found. Tests for the presence of antinuclear factor were positive.

Liver function tests and creatinine clearance tests were always normal but diminished renal plasma flow (299 cc) could be demonstrated using the P.A.H. (sodium aminohippurate) clearance.

While feeling well in herself, being slightly overweight, and able to do her housework she developed during the summer of 1971 symptomless but progressive left-sided proptosis. At the same time a slightly tender soft tissue lesion was noticed in her scalp in the left parietal region, it was attached to the underlying bone but a radiological defect could not be demonstrated. Her chest X-ray did not show any significant changes from previous films but tomography was not used.

The patient was admitted to the ophthalmology department for further investigations. While getting out of bed she fell and sustained a fracture of the neck of right femur. During surgical repair neoplastic tissue was found at the site of the fracture. Two days after the operation the patient suddenly collapsed and died.

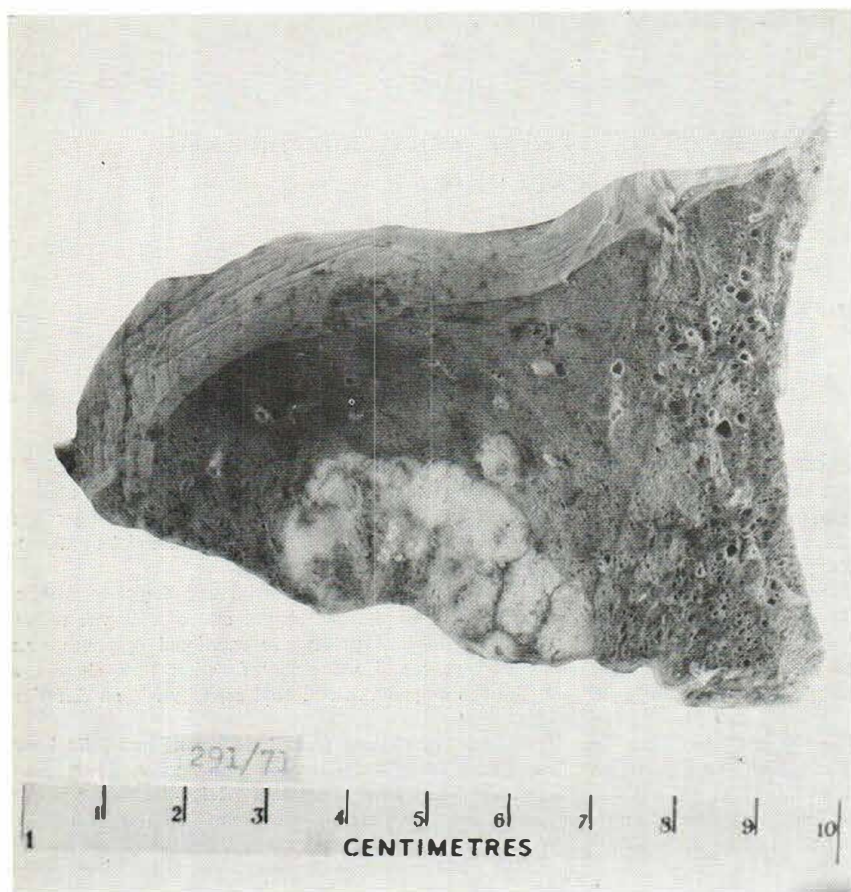


Fig. 1. Right lower lobe, showing relationship of the tumour to the fibrocystic changes.

NECROPSY FINDINGS

Lungs. The pleurae were thickened and adherent over the bases and most of the lateral surfaces. The lower lobe of the right lung contained a peripheral whitish mass, 4 cm in diameter, attached to the pleura and the chest wall and related at its lower border to a large area of fine honeycomb appearance and fibrosis (Fig. 1). It had the microscopical features of a typical oat cell carcinoma with frequent mitotic figures (Fig. 2). Tumour emboli were seen in nearby blood vessels and lymphatics. There was fibrinoid necrosis of small and medium sized arteries. The left lung showed less conspicuous fibrocystic changes at the base of the lower lobe.

The cysts were evidently derived from the air passages rather than the alveoli, being lined by respiratory epithelium, simple flattened epithelium, or by stratified epithelium with small, darker staining cells. Fibrous tissue and smooth muscle were present in the walls of these cysts as well as elastin in irregular clumps and strands.

The peribronchial and right hilar lymph nodes were enlarged by metastatic deposits forming a mass 4 cm in diameter.

Metastases. In addition to the metastatic deposits in the hilar lymph nodes, multiple metastases up to 4 cm in diameter were found in both lobes of the liver. A

solitary subcapsular deposit was present in the spleen. Large secondary deposits were also found in the skull, one in the left parietal and another in the left frontal bones. The roof of the left orbit was eroded by a secondary tumour mass largely filling the orbit and extending into the anterior cranial fossa. The pinned neck of the right femur contained a solitary secondary deposit. Microscopic metastases were also present in the right adrenal gland and the left ovary.

Skin. Microscopical examination of skin from the face, fingers, forearm, upper chest wall, abdomen and legs showed at all sites epidermal atrophy of varying degree and the dermis greatly thickened by collagen. Sebaceous glands and hair follicles were mostly absent. At some sites groups of atrophic sweat glands were invested by dense collagen. Some small dermal blood vessels showed intimal thickening and luminal stenosis with full thickness fibrinoid necrosis in places (Fig. 3).

Alimentary tract. Mild submucosal fibrosis was seen in the oesophagus and the colon. The small intestines showed merely changes of post-mortem autolysis. There was a slight macroscopic constriction of the oesophagus in its middle third.

Circulatory system. The heart was not enlarged and showed only a few areas of interstitial myocardial fibrosis

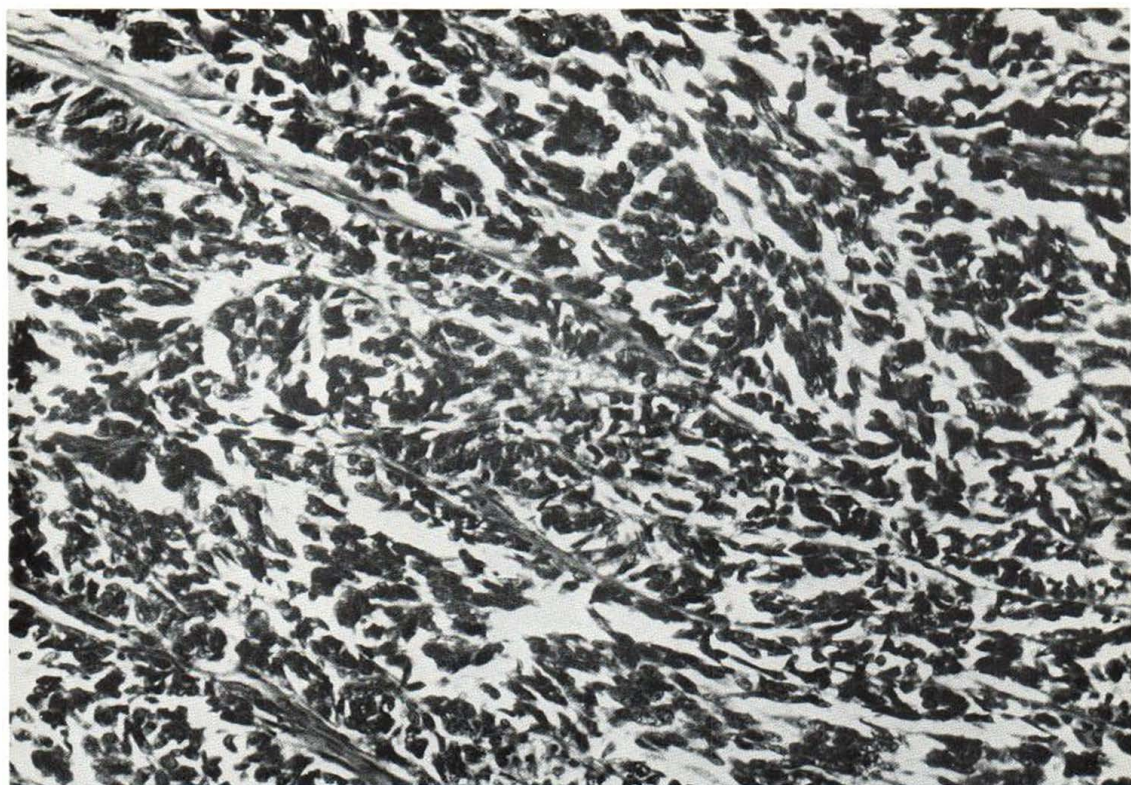


Fig. 2. Histological appearance of the oat cell carcinoma.

but no arteritis. The coronary arteries were patent and showed remarkably little atherosclerosis.

The aorta and other large vessels showed sparsely scattered atheromatous plaques with calcification in some places.

Genito-urinary system. Both kidneys were remarkably normal, showing merely mild atherosclerosis and occasional glomerular hyalinization.

DISCUSSION

This patient's rapidly growing and metastasizing oat cell carcinoma appears to have been related to her chronic pulmonary fibrosis which itself was most likely due to her systemic sclerosis. Yet the development of carcinoma of the lung, even in longstanding cases of pulmonary fibrosis, whether due to systemic sclerosis or other causes, is uncommon. Schuermann (22) failed to find any significant increase of systemic cancers in his review of 600 patients with systemic sclerosis, neither could Tuffanelli & Winkelmann (26) when reviewing 727 similar patients. Day had drawn attention to pulmonary fibrosis as a feature of

systemic sclerosis as early as 1870 (7). In their comprehensive post-mortem study of 58 cases of systemic sclerosis, D'Angelo et al. (6) found lung involvement of varying severity in 81% but no associated carcinoma.

Heppleston (12) reported 66 cases of pulmonary fibrosis with honeycombing, including 6 instances of systemic sclerosis, but none had carcinoma. However, carcinomas seemingly related to chronic pulmonary fibrosis have been reported in rheumatoid arthritis (9), the Hamman-Rich syndrome, and in fibrosis following collapse due to compression or other causes (10).

The cystic changes found in the lungs of our patient are similar to those described in systemic sclerosis by Heppleston (12) and confirmed by Richards & Milne (19), Collins et al. (5) and Caplan (4). Pulmonary epithelial proliferation may lead to adenomatosis (12) and bronchiolar carcinoma (24). This may occur in pulmonary fibrosis associated with systemic sclerosis (13, 27) but in our patient epithelial proliferation was limited to stratification of small hyperchromatic cells,



Fig. 3. Section of skin from upper chest wall, showing atrophy of the epidermis, increased dermal collagen and loss of appendages.

especially in a few foci near the tumour. Spencer & Raeburn (24) suggested that the terminal bronchiolar epithelium has proliferative potentialities from which bronchiolar carcinoma may arise as a reaction to chronic lung fibrosis, and others have accepted this view (4, 5, 18). Collins et al. (5) suggest that systemic sclerosis may lead to pulmonary fibrosis, honeycombing, adenomatosis and then carcinoma.

The mechanism by which fibrosis may induce neoplasia is uncertain. Doll (8) suggested that cholesterol, which had been shown to be present in some pulmonary scars and (20, 21) to be slightly carcinogenic, (11) might be a factor in bronchiolar carcinogenesis in scars. Simple metaplasia associated with fibrosis offers an alternative explanation (3) possibly applicable to our case with the neoplasm most likely arising from basal cells in the epithelial lining of cysts. A few small

foci of basal epithelial cells were noted in cysts adjacent to the neoplasm but the transition from benign to malignant epithelium was not observed and a fortuitous association cannot be excluded.

About one-fifth of all the oat cell tumours arise in the periphery of the lungs (23). Their oncogenesis is currently believed to be from Kultschitzky-type cells which are present in the epithelial lining of bronchi, bronchioles and distal portions of respiratory bronchioles (17). Since there was considerable doubt whether the patient with an oat cell carcinoma reported by Ashba & Ghanem (2) had systemic sclerosis, ours appears to be the first documented case of this association but there have been at least 2 other patients with other types of lung carcinoma and systemic sclerosis (1, 16) reported since Tomkin (25) reviewed the literature.

Whereas the association of lung carcinoma and

systemic sclerosis is still only tentative it is advisable to screen carefully and regularly for evidence of lung carcinoma all patients with systemic sclerosis and pulmonary fibrosis.

In view of the post-mortem findings of D'Angelo et al. (6) it is perhaps surprising that our patient, who had clinical evidence of systemic sclerosis for the last 30 years, had, apart from pulmonary fibrosis, only minimal involvement of internal organs, especially of her cardiovascular system and kidneys. It is tempting to speculate that her regular dextran infusions since 1964 had helped by improving her microcirculation.

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